MEDICAL INTELLIGENCE

CURRENT CONCEPTS IN THERAPY

Antihypertensive Agents. III.*

Edward D. Freis, M.D.†

WASHINGTON, D. C.

Sympathetic Blocking Drugs

According to present evidence nor-epinephrine is manufactured and stored in specialized chromaffin cells and granules in many parts of the body. These stores are most numerous in the intestine and spleen but are also present in other organs, including the heart.[1] The granules have been isolated from adrenergic nerves, where nor-epinephrine can be released both by nerve stimulation and by certain amines such as tyramine.[2] In laboratory animals reserpine releases and depletes the catechol amine content of the brain,[3] the heart and the adrenal medulla[4,5] and the aortic wall.[6]

These and other recent observations have led to the concept that the pressor activity of the sympathetic nervous system is mediated through the release of catechol amines in the myocardium and vascular walls and from other areas such as the adrenal into the circulating blood. According to this concept the various blocking drugs act by preventing synthesis, or release, or by depleting the body stores of pressor catechol amines.

Although this schema has the advantage of simplicity it leaves several clinical observations unexplained. For example, reserpine in the doses used in man does not appear to deactivate the sympathetic pressor system, since orthostatic hypotension and other evidences of interference with sympathetic vasoconstrictor reflex responses are absent. The monamine oxidase inhibitors, which in animals prevent the destruction of nor-epinephrine, and therefore should raise blood pressure, produce depressor effects and orthostatic hypotension in man.[7] Alpha-methyldopa inhibits the synthesis of nor-epinephrine, but the antihypertensive effects in patients is not explained entirely by this mechanism.[8] Guanethidine reduces the catechol amine content of the heart and aorta of animals,[9] but hypotensive doses in man were unassociated with any inhibition of the pressor response to tyramine.[10] These discrepancies point up some of the difficulties that the physician faces in attempting to correlate clinical experience with current pharmacologic theory.

Ganglion-Blocking Drugs

The ganglion-blocking drugs competitively inhibit the action of acetylcholine, which is the chemical mediator for the transmission of nerve impulses through all autonomic ganglions, parasympathetic as well as sympathetic.[11] Since sympathetic vasoconstrictor nerves are distributed to venules and veins, as well as to the arterioles, there is not only a decrease in arteriolar resistance but also an increase in the venous capacity of the peripheral vascular beds. As a result of the latter, filling pressure in the right side of the heart falls, and the cardiac output decreases,[12] except in patients with congestive heart failure, in whom the cardiac output increases because of the beneficial effects of the reduction in both aortic pressure and filling pressure in the right side of the heart.[13] There also is a redistribution of the cardiac output, with a greater portion going to the extremities, especially the skin, and a smaller part to the splanchnic circulation.[14]

The ganglion-blocking drugs most frequently used clinically are pentolinium tartrate (Ansolysen), chlorisondamine (Ecolid) and mecamylamine (Inversine). Although the last has the theoretical advantage of being more completely absorbed on oral administration, the double-blind study of the Veterans Administration did not indicate that any one of these agents was superior to the others in either hypotensive effectiveness or reduced incidence of side effects.[15]

Ganglion-blocking drugs are disappearing from clinical practice for the reason that most patients prefer agents, such as guanethidine, that specifically inhibit the sympathetic and spare the parasympathetic nervous system. The side effects of parasympathetic blockade produced by the ganglion-blocking drugs, such as dry mouth, paralysis of visual accommodation, constipation and failure of erection, are especially disturbing. It is true, however, that the incidence and severity of such side effects have been considerably reduced since the advent of chlorothiazide, which greatly potentiates the antihypertensive effects of the ganglion-blocking drugs, thereby permitting blood-pressure control with smaller, less blocking doses.[16]

Guanethidine

Guanethidine (Ismelin) produces a specific blockade of the sympathetic nervous system by acting on the endings of the adrenergic nerves.[16] Part of its action as already mentioned seems to be connected with depletion of tissue catechol amines. When administered intravenously in man there is a transient pressor effect,[17] often with an increase in cardiac output[10] that could be due to release of catechol amines. This is quickly followed by a prolonged depressor effect, with orthostatic hypotension and other evidences of inhibited vasoconstrictor responses.[17] Both the cardiac output and the total peripheral resistance are reduced,[18] and, as with the ganglion-blocking drugs, the splanchnic blood flow decreases considerably.[10]

In contrast to the ganglion-blocking drugs, but

*From the Veterans Administration Hospital and the Department of Medicine, Georgetown University School of Medicine.

†Senior medical investigator, Veterans Administration; associate professor of medicine, Georgetown University School of Medicine.

Reprinted from the *New England Journal of Medicine*
266:775-777 (April 12), 1962

similar to reserpine, guanethidine has a very long duration of action, lasting up to five to seven days.[19] Furthermore, tolerance does not occur. Consequently, once the dose has been adjusted, the antihypertensive effect characteristically exhibits less fluctuation than with the ganglion-blocking drugs. Unlike orally administered reserpine, however, which has a relatively weak hypotensive action, orally administered guanethidine is as potent as any antihypertensive drug available today. Because of the long duration of action the daily doses are cumulative over a period of approximately a week. To minimize hypotensive reactions at least this period should be permitted, whenever possible and practical, for observation of results before the doses are further elevated.

The principal side effects of guanethidine are orthostatic hypotension, diarrhea and failure of ejaculation. Parasympathetic blocking agents or paregoric will help control the diarrhea. As chlorothiazide enhances the antihypertensive effect it can be added with advantage when any of the side effects mentioned above are troublesome since such an addition will usually permit a considerable reduction in the dose requirement for guanethidine.

The effective dose of guanethidine is extremely variable from one patient to another, ranging from as little as 10 to more than 300 mg. per day. Although the initial adjustment period requires care and flexibility the long-term results with guanethidine have been gratifying in most patients, usually with disappearance of all side effects, including orthostatic faintness, and maintenance of a continued antihypertensive effect without further adjustments. Patients coming to emergency surgery while taking this drug may require nor-epinephrine support. Guanethidine should be withdrawn several weeks before elective operations.

Other Blocking Drugs

Bretylium tosylate (Darenthin) also produces a selective block of the sympathetic nervous system.[20] The development of tolerance and the frequent occurrence of pain over the parotid area during eating have limited its clinical usefulness.

Alpha-methyldopa (Aldomet) inhibits the decarboxylation of dopa to dopamine, which is believed to be a precursor of nor-epinephrine. It seems probable, however, that the mode of action of alpha-methyldopa is more complex than simple inhibition of nor-epinephrine synthesis.[7] Clinically, the drug lowers blood pressure without greatly interfering with sympathetic vasoconstrictor reflexes; orthostatic hypotension is not as prominent as with other blocking agents. Except for transient induction of sleepiness and occasional, moderate orthostatic hypotension alpha-methyldopa has been remarkably free of disturbing side effects. Although the majority of the hypertensive patients exhibit a significant and sometimes striking hypotensive response to doses of approximately 1 to 2 gm. per day there are others who appear to be quite resistant to the antihypertensive effects of the drug. Although this agent is still under clinical investigation the lack of toxicity and freedom from annoying side effects suggest that it may be clinically useful.

A number of *amine oxidase inhibitors* have been tried in the treatment of hypertension.[7] Most of these compounds belong to the hydrazine group, which have demonstrated hepatic and central-nervous-system toxicity. Recently, pargyline, which although not a hydrazine exhibits amine oxidase inhibition, has been developed. Preliminary clinical experience indicates that it is a potent antihypertensive agent and induces orthostatic hypotension.[21]

The past few years have seen the advent of a variety of blocking agents with specific inhibiting effects on the sympathetic nervous system. Of these, guanethidine has become established in the treatment of moderately severe and severe hypertension. Certain of the others appear to hold promise but have not yet weathered the test of long-term clinical trial. All the blocking drugs have in common a wide range of dose requirement from one patient to another. The more potent the antihypertensive effect of a blocking agent, the greater the need for careful titration. In the management of severe hypertension, however, they remain the mainstays of antihypertensive treatment.

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